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BLOCKADE OF CHEMOKINE: GLYCOSAMINOGLYCAN (GAG) (GLYCOCALYX) BINDING IN THE RENAL DONOR ORGAN SIGNIFICANTLY REDUCES TRANSPLANT REJECTION AND VASCULAR INFLAMMATION

Poster Contributions
Poster Hall B1
Saturday, March 14, 2015, 10:00 a.m.-10:45 a.m.

Session Title: New Findings in Vascular Inflammation and Endothelial Function
Abstract Category: 45. Vascular Medicine: Non Coronary Arterial Disease
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Authors: *Alexandra R. Lucas, Sriram Ambadapadi, Hao Chen, Donghang Zheng, Dara Wakefield, William Clapp, University of Florida, Gainesville, FL, USA, Malcolm Randall VA Medical Center, Gainesville, FL, USA*

Background: Innate immune (inflammatory) cells are activated early after allograft transplant and are active long term, inducing transplant vasculopathy, a leading cause of late transplant loss. Treatment of TV remains limited and there is a need for treatments to prevent transplant loss. The connective tissue matrix, specifically glycosaminoglycans (GAGs) in the endothelial glycocalyx, induce inflammatory cell activation through chemokine binding to form a signal array to attract monocytes and T cells. Recent studies predict a GAG blueprint that directs chemokine mediated cell migration.

Methods: We investigated early chemokine: GAG interactions after renal allograft transplantation using heparin sulfate HS- GAG deficient (KO) donor mice and a viral chemokine modulating protein (CMP) that blocks chemokine: GAG interactions, M-T7, that blocks C, CC and CXC chemokine: GAG interactions. Methods - 96 mice had C57Bl/6 (B6) to BALB/c renal allograft transplants; 48 had WT B6 transplant and 48 had Ndst1 HS-GAG KO in endothelial cells and myeloid precursors. Mice were treated for 10 days with either M-T7 or one of three point mutations (100ng/gm) with differing inhibitory actions for chemokine: GAG interactions, but no immunosuppressant.

Results: Ndst1 HS-GAG KO in donor organs significantly reduced overall acute rejection by histology score ($P < 0.0001$). M-T7 also significantly reduced rejection and vasculitis in B6 allografts ($P < 0.0001$), but lost activity in Ndst1 KO allografts. Treatment with M-T7 Point mutations, E209I and R171E retained activity but R171E was inactive in Ndst1KO; F137D was inactive. CD3 + T cells were significantly reduced ($P < 0.0001$) in Ndst1 KO donor grafts and after M-T7 treatment in WT B6 transplants. PCR array analysis of HS GAG KO transplants and in B6 transplants with M-T7 treatment demonstrated significant reductions in inflammatory cytokines, chemokines and apoptotic pathways.

Conclusion: These studies indicate a major role for donor organ chemokine: GAG interaction in chronic allograft rejection and vascular disease, providing a wide range of new potential therapeutic options targeting donor allograft HS-GAG: chemokine interactions.